

A. The Present Invention

Radiosensitizers are chemical agents that act to increase the lethal effect of subsequent radiation treatment to a cell. For effective radiation therapy of a tumor, it is desirable to have a radiosensitizer present in the tumor in a high concentration.

The present invention relates to a method of delivering a radiosensitizer to achieve this goal. In the method, the radiosensitizer is administered to a tumor-bearing patient in the form a liposome composition. More particularly, the liposomes are comprised of (i) a vesicle-forming lipid; (ii) between 1-20 mole percent of a vesicle-forming lipid derivatized with a hydrophilic polymer chain, and (iii) between 1-15 mole percent of a radiosensitizer derivatized with a lipid moiety linked to the radiosensitizer. This method of delivery allows for effective accumulation of the radiosensitizer in the tumor by virtue of the hydrophilic polymer chains, which impart a long blood circulation lifetime to the liposomes. The lipid moiety linked to the radiosensitizer ensures that the agent remains associated with the liposomes during circulation in the blood stream.

B. The Cited Art

MARTIN ET AL. describe liposomes having a coating of polymer chains for administration of an anti-tumor compound to a solid tumor via the bloodstream.

Martin et al. fail to show or suggest a liposome that includes in the lipid bilayer a radiosensitizer derivatized to a lipid moiety.

MORI ET AL. relate to a liposome composition specifically designed to target the lung. The liposomes include an antibody that acts as a homing device for lung epithelial tissue, for delivery of the lipophilic prodrug dipalmitoyl-fluoro deoxyuridine (dpFUDR) to the organ.

Mori et al. fail to show or suggest liposomes that include a lipid derivatized with a hydrophilic polymer.

KASSIS ET AL. relate to a method for treating a tumor by administering a radiohalogenated pyrimidine compound, such as iodo deoxyuridine, IudR, in a saline vehicle.

Kassis et al. nowhere show or suggest a liposome composition.

C. Analysis: Rejection over Martin et al. in view of Mori et al. Fails Since there is no Motivation to Combine the Cited References

1. Legal Standard

"The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP § 2143.01. "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." M.P.E.P. § 2143.01.

2. Combination of Martin et al. and Mori et al.

It is the Examiner's position that it would have been obvious to one of ordinary skill to either (1) use the radiosensitizer of Mori et al. as the anti-tumor agent in the liposome composition of Martin et al. because of the effectiveness of the radiosensitizer, or (2) use the lipid derivatized polymer of Martin et al. in the liposome composition of Mori et al. to increase the blood circulation time of the liposomes of Mori et al.

Applicants disagree with these assertions for the following reasons.

i. Regarding the Examiner's First Assertion

As noted above, obviousness is not established unless there is some objective reason to combine the teachings of the references. The Examiner asserts that the objective reason to modify Martin et al. to include the radiosensitizer of Mori et al. is found in the fact that Mori et al. teaches the effectiveness of

radiosensitizers as anti-tumor agents. There are two problems with this assertion.

First, Martin *et al.* is specifically concerned with providing liposomes that evade uptake by the reticuloendothelial system (RES) to achieve a long blood circulation lifetime for extravasation into a tumor. Incorporation of a lipid-derivatized radiosensitizer into the lipid bilayer of the liposomes results in radiosensitizer molecules extending from the external surface of the liposomes. The presence of radiosensitizer molecules on the outer liposome surface compromises the evasion properties of the liposomes, since the agent may not be completely masked by the polymer chains. Since the agent is not masked from recognition, the liposomes are susceptible to recognition and removal by the RES. Therefore, modification of Martin *et al.* to include the lipid prodrug of Mori *et al.* would compromise the desired extended blood circulation lifetime of the liposomes, defeating the purpose of the liposome composition of Martin *et al.*

Second, Mori *et al.* teaches that dpFUDr when incorporated into liposomes has a decreased therapeutic index due to increased toxicity (page 454, Col. 2, last 5 lines). Modification of lipid compositions, drug/lipid ratios, and particles sizes of liposomes failed to improve the therapeutic index of dpFUDr incorporated into liposomes (sentence bridging pages 454-455). Mori *et al.* assert that "dpFUDr was effective in prolonging the survival of mice only when it was incorporated into 34-A liposomes" (page 455, second paragraph, where 34-A is the antibody homing agent). Fig. 5 in Mori *et al.* affirms this feature, where the survival of mice treated with dpFUDr liposomes and dpFUDr-liposomes including an antibody targeting agent was compared, and only mice treated with targeted liposomes showed any significant improvement in survival time.

Thus, one of skill in the art finds no motivation in Mori *et al.* to incorporate a lipophilic radiosensitizer into liposomes, since such a composition would have a decreased therapeutic index and offers no significant advantage in survival over a simple

emulsion of the lipophilic radiosensitizer or a saline composition of the radiosensitizer.

Accordingly, for the two reasons just discussed, Applicants submit that there is no motivation to modify Martin et al. to include the lipophilic radiosensitizer of Mori et al.

b. Regarding the Examiner's Second Assertion

The Examiner also asserts that it would have been obvious to one of ordinary skill to (2) use the lipid derivatized polymer of Martin et al. in the liposome composition of Mori et al. to increase the blood circulation time of the liposomes of Mori et al. This assertion fails for at least these reasons.

First, Mori et al. is concerned with providing a liposome composition that targets an organ, such as the lung, by virtue of an antibody attached to the liposome surface. The antibody must be 'accessible' or 'unhindered' in order to achieve a targeting effect. It is clear from the teaching in Mori et al. that hindering the accessibility of the antibody was a concern, since on page 451, Col. 2, final paragraph, Mori et al. comment on the fact that '3 mole percent of dpFUdR does not alter 34A-liposomes homing to the lung'. Modification of the targeted liposomes to include additional surface agents, such as a lipid-anchored polymer chains, would likely reduce the ability of the surface attached antibody to target the lung. For this reason, modification of the liposomes described by Mori et al. to include a polymer-derivatized lipid does not make sense.

Second, addition of a lipid-derivatized polymer chain will alter the biodistribution of the liposomes, extending the blood circulation lifetime and ultimately delay accumulation, if it occurs at all, of the liposomes in the lung. The alteration in biodistribution combined with poor accessibility of the targeting agent would render the composition of Mori et al. unsatisfactory for its intended purpose of targeting to an organ, such as the lung.

Further evidence that modification of the liposomes with a

lipid-derivatized polymer chain is not a desirable modification, is found in the fact that Mori et al. is not concerned with targeting to a tumor but to an organ (page 455, Col. 2, last paragraph). Mori et al. state that the advantage of organ-specific immunoliposomes is delivery of the drug to normal cells, not to tumor cells. Modification of the liposomes to include a lipid-derivatized polymer chain would alter the biodistribution and targeting capability of the liposomes, negating the features explicitly desired by Mori et al.

Accordingly, Applicants respectfully request withdrawal of the rejection over Martin et al. in view of Mori et al. under 35 U.S.C. §103.

C. Analysis: Rejection over Martin et al. in view of Mori et al. and in view of Kassiss et al.

The arguments above apply equally to the rejection based on Martin et al. in combination with Mori et al. and Kassiss et al. Namely, modification of the liposomes of Martin et al. to include the lipophilic prodrug of Mori et al. does not make sense, since such a modification would compromise the RES-evading properties of the liposomes in Martin et al. Similarly, modification of Mori et al. to include a lipid-derivatized polymer of Martin et al. makes no sense, since such a modification would compromise the targeting ability and biodistribution properties of the Mori et al liposomes and render them unsatisfactory for the purpose of targeting an organ.

Kassiss et al. does not make up for these deficiencies. Kassiss et al is limited to a teaching of administering a radiosensitizer in the form of a saline solution, and is silent on liposome compositions.

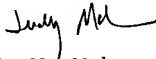
Accordingly, Applicants respectfully request withdrawal of the rejection over Martin et al. in view of Mori et al. and in view of Kassiss et al. under 35 U.S.C. §103.

II. Conclusion

In view of the above remarks, Applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

The Examiner is invited to contact Applicants' representative at 650-838-4402 if needed to further prosecution of this application.

Respectfully submitted,



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